Remarks/Arguments

Claims 44 - 46, 49 and 52 - 60 are pending in this application.

Amendments

Claims 44-46 and 49 were previously allowed. New claims 52 - 60 correspond to claims 39 - 43, and 50 - 51. Previous claims 39 - 43 and 50 - 51 were canceled by Applicants upon the indication of allowance of claims 44 - 46 and 49 and the further indication that the Response to Final Office action filed October 21, 2003 would not be entered.

Applicants subsequently filed a Request for Continuing Examination. In the Request for Continuing Examination, Applicants requested that the Response to Final Office Action filed October 21, 2003 be entered and considered.

No new matter is added by these amendments.

Priority

Based on the ability of the claimed polypeptides to inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, which was disclosed in application PCT/US00/04414, the Examiner accorded February 22, 2000 as the earliest priority date to the present application.

As discussed in the arguments below, the gene amplification data, which provide patentable utility for the PRO211 polypeptides claimed, were first disclosed in application PCT/US98/18824, filed on September 10, 1998. Accordingly, the effective priority date of the present application is September 10, 1998.

35 U.S.C. §112, First Paragraph, Rejections

Canceled claims 39-43 and 50-51 were previously rejected under 35 U.S.C. §112, first paragraph, for lack of enablement allegedly because a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:2 which isolated polypeptide inhibits VEGF stimulated proliferation of adrenal cortical capillary

endothelial cells, does not reasonably provide enablement for a polypeptide not identical to at least the mature form of SEQ ID NO:2 which does not have this activity.

Applicants wish to claim priority to PCT/US98/18824, filed September 10, 1998 and accordingly wish to rely on the gene amplification data for patentability.

Claims 52 - 60 are the same as previously canceled claims 39 - 43 and 50-51. Accordingly, Applicants will respond to this previous rejection.

Claims 52 - 56 recite that the polypeptides are associated with the formation or growth of lung or colon tumors. The Examiner has previously stated that the increased copy of DNA allegedly does not provide a readily apparent use for the polypeptide because 35 U.S.C. §101 clearly states that the invention must be useful in currently available form, which precludes any further experimentation to establish utility of the claimed invention.

The specification discloses a substantial, specific and credible utility for the PRO211 polypeptide. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of all pending claims.

A Declaration under 37 C.F.R. §1.132 by Dr. Goddard was previously filed with the October 21, 2003 response. A second Declaration under 37 C.F.R. §1.132 by Dr. Ashkenazi was also filed with the October 21, 2003 response. Applicants enclose herewith a third Declaration under 37 C.F.R. §1.132 BY Dr. Paul Polakis.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines, 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 USC 101 if it has at least one asserted "specific, substantial and credible utility". In explaining the "substantial utility" standard MPEP 2107.01 cautions that Office personnel must be careful not to interpret the phrase 'immediate benefit to the public" to mean that products or services based on the claimed invention must be "currently available" to the public. Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient at least with regard to defining a "substantial utility". Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in MPEP 2107II(B) gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose...and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility".

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible". Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record...that is probative of the applicant's assertions." (MPEP 2107 II (B)(1)(ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the gene amplification data provided in the present application as explained below and in the Goddard Declaration, the Ashkenazi Declaration and the Polakis Declaration is sufficient to establish a specific, substantial and credible utility for the PRO211 polypeptide to which the claimed antibodies are directed. Accordingly, the claimed invention is enabled.

The Declaration by Audrey Goddard clearly establishes that the TaqMan™ realtime PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. The Declaration confirms that based on the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO 211 is a diagnostic marker of human lung and colon cancer.

Applicants would direct the Examiner to pages 222, line 44 to page 223, line 223 which states "The results of the TaqMan ™ are reported in delta (Δ) CT units. One unit corresponds to 1 PCR cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold..." It is well known that gene amplification occurs in most solid tumors and generally is associated with poor prognosis. As shown in Example 92 and Table 9, PRO211 showed approximately 2-5 fold amplification in 30 primary tumors. The Goddard Declaration confirms that based upon the gene amplification results set forth in Table 9 one of ordinary skill would find it credible that PRO211 is a diagnostic marker of human lung cancer. Accordingly, PRO211 polypeptides would be useful to generate antibodies as diagnostic reagents for diagnosing lung tumors.

In his Declaration, Dr. Ashkenazi confirms that even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example by the reverse transcriptase TaqMan™PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy.

The working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

As Dr Ashkenazi explains in his Declaration,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO211 polypeptide and antibodies binding to it have a substantial specific utility.

Further, Applicants submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations

(deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO211 gene, that the PRO211 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO211 polypeptides and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Accordingly, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO211 polypeptide and for the antibody that specifically binds to PRO211. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed polypeptides at the time of filing.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C5**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 18, 2004

By: Leslie Mooi
Leslie A. Mooi (Reg. No. 37,047)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025
Direct Dial: (650) 324-6786
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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